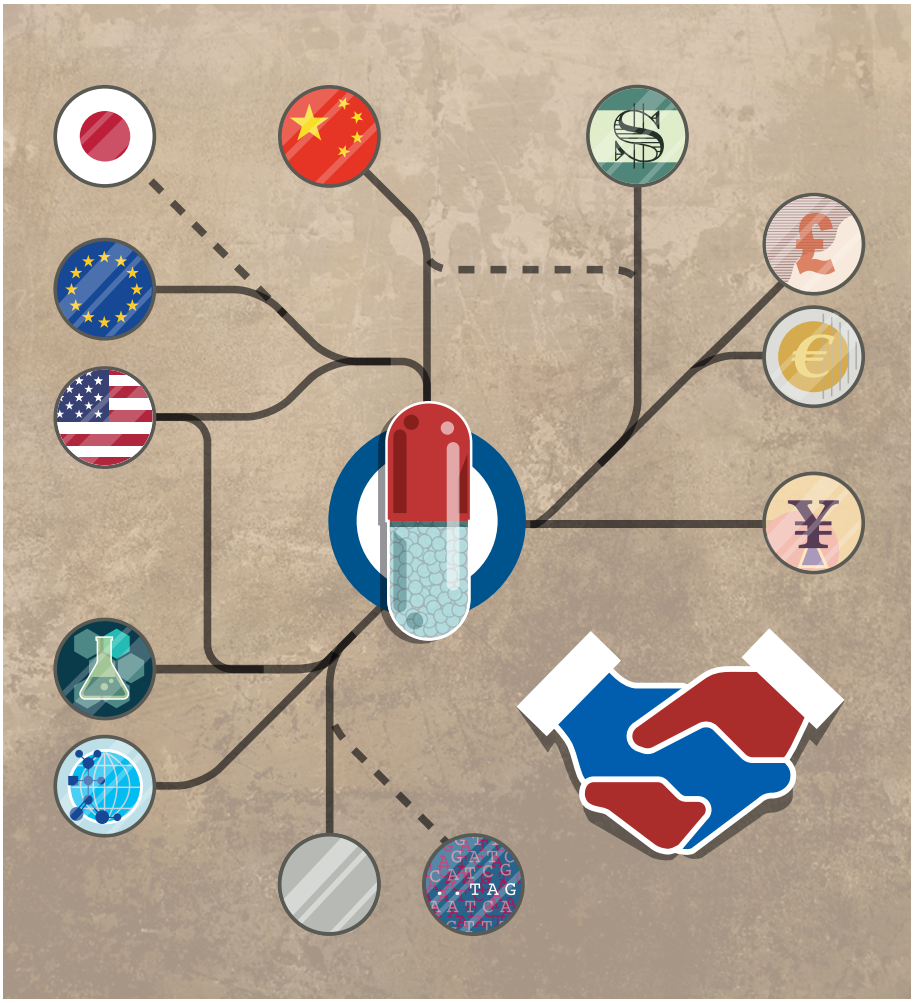


NIK SPENCER

DRUG DEVELOPMENT

Time for teamwork

In the face of more drug-resistant bugs and fewer new drugs, partnerships promise a resurgence of antibiotics.

BY MIKE MAY

We are facing a bacterial-resistance catastrophe. In the United States, germs that are resistant to antibiotics infect at least 2 million people every year[1], making these infections more commonplace in the US population than cancer. At least 23,000 of those infected with antibiotic-resistant germs die. According to the US Centers for Disease Control and Prevention (CDC), intestinal infections with *Clostridium difficile* caused 400% more deaths in 2007 than in 2000, "in part because of a stronger bacteria strain that emerged"[1]. Likewise, the World Health Organization found that reported cases of multidrug-resistant tuberculosis in Africa soared[2] from 2,445 in 2005 to 18,146 in 2012 — an increase of nearly 650%. Daria Hazuda, who is head of discovery for infectious disease at Merck Research Laboratories in West Point, Pennsylvania, warns that "about half of today's infections are caused by strains of bacteria that are resistant to existing antibiotics."

Despite what Hazuda points out to be a "significant unmet medical need for new antibiotics", the pipeline for such drugs has slowed to a drip over the past 30 years. Between 1980 and 1984, the US Food and Drug Administration approved 20 new antibiotic drugs, but between 2005 and 2009 only three new antibiotics were approved. This crash in approvals reflects the plummeting productivity in the antibiotic-development sector of the pharmaceutical industry. Companies picked the easy fruit from the tree long ago, so new drugs have become harder to find. Also, the growing resistance in bacteria means that new drugs need to work in different ways, increasing the challenge even further.

The problem is rooted in economics. It takes hundreds of millions of dollars to develop any new drug. Recouping that investment is particularly hard to do with an antibiotic, largely because they are not valued highly enough to create a reasonable return. Brad Spellberg, who studies infectious diseases at the David Geffen School of Medicine at the University of California, Los Angeles, sums up the problem: "We will pay US$50,000 for a course of cancer chemotherapy that prolongs life by 3 months, but we don't want to pay more than $100 for a course of antibiotics that cures the target infection."[3] In the United States, insurance companies do most of the paying and often set the fees that can be reimbursed for specific drugs. Nonetheless, Spellberg suggests that the public are prepared to spend more on chemotherapy than on antibiotics. "People are terrified of cancer, but not of infections," he says.

The short duration of antibiotic prescriptions, usually lasting only a week or two at a time, makes it hard for these drugs to compete with the economic returns of medications that can be prescribed for life, such as treatments for diabetes. In fact, Merck's leading diabetes medication outsold its top antibiotic by about 7.5 times for 2009–2012 (see 'Diabetes far out-earns infections'). Such disparities could become even more pronounced as experts around the world preach the need to use even fewer antibiotics, prescribing them only when absolutely needed, to help slow down the development of resistance.

So, from a strictly rational business point of view, the pharmaceutical industry's retreat from antibiotics makes sense. David Payne, who leads the GlaxoSmithKline (GSK) antibiotics research unit in Collegeville, Pennsylvania, summarizes the issue: "I think the reason some companies move out of antibiotics is because there are other areas where they can get a greater return on investment."

STAY OR GO?

Pharmaceutical companies respond differently to the economic challenge of developing new antibiotics. For instance, Pfizer, which is based in New York City and was ranked by Forbes as the world's biggest drug company in 2013, closed its antibiotics research and development (R&D) facility in 2011. Apparently,

Pfizer has no plans to get back in the antibiotics business. Dean Mastrojohn, director of Pfizer's global media relations, says: "We will no longer conduct small-molecule R&D or business development activity aimed at in-licensing R&D-stage antibacterials and are seeking external partners for the few early stage programmes we had." So the world's biggest player seems to be set on staying out of antibiotics development.

Some of the pioneers in antibiotics plan to stay in this business, however. Merck, for example, was involved from the start, supplying the penicillin that was used for the first treatment of a patient with antibiotics in 1942.

Today, Merck hopes that advanced tools will speed up the development of medicines that fight infections. As Hazuda says: "We can use several technologies in high-throughput ways to enable us to figure out the mechanism by which new agents are working." Specifically, high-throughput sequencing, genomics and proteomics can reveal how an agent affects a specific bacterial target. "Then you can use that information to see if it's a new mechanism of action," Hazuda says. These tools might improve the profitability of creating new antibacterials. As an example, Merck has a monoclonal antibody, MK-3415A, in phase III trials for *C. difficile*, which the CDC blames for 14,000 deaths a year in the United States.

Roche closed its antibiotics division in 1999. "There was little reason to keep making new antibiotics then, because we thought we had more than we needed," explains Janet Hammond, head of Roche's Infectious Diseases Discovery and Translational Area in Basel, Switzerland. Recently, however, the company has started looking into this area again: "In the last year, we made a decision that we would go back into antibiotics," says Hammond. As part of its return, Roche plans to combine antibiotics research with other areas of expertise. "We are also strong in diagnostics," Hammond explains, and such tests could be used, for example, in clinical trials to more quickly assess the potential of a drug, potentially reducing the cost of development.

The increasing concern over infections has also spawned a range of antibiotics-focused companies. The list of specialists includes the following, among others: Achaogen in South San Francisco, California; Cempra in Chapel Hill, North Carolina; Hsiri Therapeutics in King of Prussia, Pennsylvania; and Qilu Antibiotics Pharmaceutical in Jinan City, China.

But even a specialist probably won't see a fast fortune from an antibiotic. More than a decade ago, Cubist Pharmaceuticals, based in Lexington, Massachusetts, received its first drug approval for Cubicin (daptomycin), which was the first of the so-called lipopeptide agents. It inserts itself into a bacteria's membrane and creates holes in it, killing the cell. This antibiotic can be used for serious infections, such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). It turns out that making an antibiotic that treats such a dangerous infection, especially an infection that resists most existing medicines, can eventually generate big sales. In 2013, Cubicin gained blockbuster status by generating more than $1 billion in sales.

"The industry was dormant and we are using public–private partnerships to reinvigorate it."

Cubist used this commercial success to fund more research and acquire companies that could contribute to its antibiotics pipeline. In 2013, for example, Cubist acquired Optimer Pharmaceuticals and Trius Therapeutics. At the time of writing, Cubist has two antibiotics on the market and several more in clinical trials. As chief scientific officer Steve Gilman says: "We're leveraging our experience with Cubicin to develop new antibiotics." Such a concerted focus could be the key to success in this area.

EMPOWERED BY PARTNERS

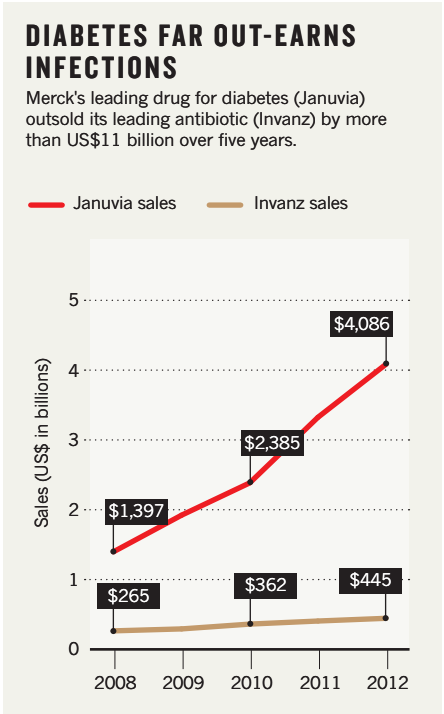
Despite the economic success of Cubicin, the real key to energizing tomorrow's antibiotics arsenal could well come from public–private partnerships, in which government-funded departments or organizations provide financial and technical support to pharmaceutical companies. "We approached this looking at an industry that had become dormant, and we are using public–private partnerships to reinvigorate it," says Robin Robinson, director of the US Biomedical Advanced Research and Development Authority (BARDA). In particular, Robinson says that the US government provides a stable funding partner and technical expertise. "With antibiotics, these are major issues for industry."

As an example, Robinson's team works with GSK. "We are on a board with GSK to look at the entire antimicrobial pipeline and help them make decisions about how they allocate their money and how we allocate ours going forward," he explains. So rather than providing money and then walking away, BARDA has an ongoing advisory role in the research and regulatory decisions related to GSK's antibiotics pipeline.

In Europe, the largest public–private partnership for developing new medicines is the Innovative Medicines Initiative (IMI), based in Brussels, Belgium. The IMI receives half of its funding from the European Union and half from pharmaceutical companies, so teamwork is baked into the cake.

The IMI recently launched a collaborative project as part of its 'New Drugs for Bad Bugs' programme, which is focused specifically on creating new business models for developing antibiotics. As Angela Wittelsberger, scientific project manager in charge of antibiotics at IMI, explains: "This brings stakeholders together who are not used to working together, including people from public health, academia, large and small industries, reimbursement agencies and government bodies." The pharmaceutical companies form the initial consortium, then the IMI invites proposals to select collaborators from the public sector, including universities, regulators and patient groups. This disparate collection of organizations will explore ways to efficiently and economically produce new antibiotics, hoping that teamwork will improve finances and innovation. Many international pharmaceutical companies — including AstraZeneca, GSK, Cubist and others — have already shown interest.

Although it is still in development, Wittelsberger sees a bright future for the programme. "The large realization from the pharmaceutical industry that this is something they should engage in and do collaboratively with their competitors all together is exciting," she says. Such a broad level of teamwork might be the best hope — maybe the only hope — of fighting the growing threat from antibiotic-resistant bacteria. ■



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